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Thromboxane in Complicated and Uncomplicated Hypertension

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Abstract

This work comprised seventy seven hypertensive patients as well as fourteen healthy normotensive age matched subjects as a control group they were categorized into uncomplicated hypertension (Group I), hypertension complicated by coronary artery disease (Group II), and hypertension complicated by acute cerebral infarction (Group III). They were submitted to full clinical assessment, ECG, abdominal sonography, routine laboratory investigations, plasma renin activity, plasma thromboxane B2 and 6-Keto-prostaglandin F1α Echocardiography and C.T. brain scan were done whenever indicated. 6-Keto-prostaglandin F1 α level was significantly reduced in group I, while thromboxane B2 level showed no difference, however, the ratio TXB2/6.K.PGF1 α was significantly higher when compared to controls. In hypertensive patients complicated by coronary artery disease (group II) while both thromboxane B2 and 6-Keto-prostaglandin F1 α levels showed no significant difference compared to either controls or group I, the ratio TXB2/6.K.PGF1 was significantly higher. In hypertensive patients complicated by cerebral infarction (group III) both thromboxane B2 level and the ratio TXB2/6.K.PGF1 α level were significantly higher when compared to either controls, group I or group II patients, however, 6.K.PGF1 α showed no significant difference when compared to these groups. In the three studied groups both TXB2 and 6.K.PGF1 α were positively correlated with either systolic, diastolic or mean blood pressure. Also TXB2 and 6.K.PGF1α levels were positively correlated to each other. In our study, the plasma renin activity showed no significant difference between the controls and any of the three studied groups.

Introduction

ESSENTIAL hypertension is a common cardiovascular disease characterized by increased peripheral resistance and increased incidence of arterial occlusive disease. Devasting complicatins such as coronary artery disease and cerebrovasscular stroke are common in patients with untreated hypertension[1].

Thromboxane A2 and prostacyclin, eicosanoids derived from arachidonic acid, have oppsing effects on vascular smooth muscles and platelets. An imbalance in the biosynthesis of these mediators could therefore influence both vascular tone and predisposition to thrombosis in patients with essential hypertension[2].

Evidence from recent studies suggest that thromboxane synthase inhibitors, have considerable importance in the prevention of hypertensive complications. Thus, it seems prudent to investigate the pathophysiological role of these prostaglandins in the development of hypertension as well as its vascular complications[3].

The aim of the work is to study the plasma level of thromboxane B2 (stable metabolic product of thromboxane A2) and 6.Keto-prostaglandin F1 (stable metabolic product of prostacyclin) in hypertensives (complicated and uncomplicated).

Material and Methods

The present study was carried out on seventy seven hypertensive patients (34 men and 43 women) ranging in age from 40 to 65 years (51.87 ± 1.05 years). Fourteen healthy normotensive age-matched (50.57 ± 5.94 years) subjects (9 men and 5 women) were taken as a control group.

They were subjected to : Full history taking, full clinical examination, electrocardiographic study, abdominal ultrasonography, echocardiography when indicated and CT scan of brain when indicated. Routine laboratory investigations including: Complete blood picture and platelet count, blood urea and serum creatinine, fasting and 2 hour postprandial serum glucose, serum lipid profile (serum cholesterol and triglycerides), as well as serum uric acid. Radioimmunoassay studies, plasma renin activity[4], plasma thromboxane B2 concentrations[5], and plasma 6 - keto - prostaglandin F1 α concentrations[5].

Patients were considered to have hypertension when their diastolic blood pressure was in excess of 90 mmHg measured in more than two different occasions in supine position. Mean arterial blood pressure was calculated by the equation :

$$MAP = DBP + SBP - DBP/3.$$

Patients were categorized into three main groups :

Group I : uncomplicated hypertension. included 38 patients (14 males and 24 females) with a mean age of 50.76 ± 7.26 years.

Group II : hypertension complicated by ischemic heart disease. Included 13 patients (6 males and 7 females) with a mean age of 52 ± 6.67 years.

Group III : hypertension complicated by cerebrovascular stroke. Included 26 patients (14 males and 12 females) with a mean age of 52.85 ± 7.96 years.

Results

The results are showen the tables (I & II) and Figures (I & II).

Table (1) : Statistical Analysis Comparing the Mean Values of Plasma Renin Activity, Thromboxane B2 (TXB2), 6.Keto. Prostaglandin F1 α (6.K.PGF1 α) and the Ratio TXB2/6.K.PGF1 α Between the Control Group and the Patient Groups.

Group	Plasma Renin Activity (ng/ml/h)	Plasma TXB2 level (pg/ml)	Plasma 6.K.PGF1 α level (pg/ml)	Ratio TXB2/6.K.PGF1 α
Control Group				
— Mean	1.57	79.28	51.57	1.55
— S.D.	0.93	32.91	21.66	0.07
Group (I)				
— Mean	1.28	80.72	43.08	1.87
— S.D.	0.7	19.62	9.03	0.11
— P1	N.S.	N.S.	<0.05	<0.001
Group (II)				
— Mean	1.17	84.04	44.77	1.87
— S.D.	0.9	22.00	9.63	0.16
— P2	N.S.	N.S.	N.S.	<0.001
— P4	N.S.	N.S.	N.S.	N.S.
Group (III)				
— Mean	1.52	136.83	46.42	2.92
— S.D.	0.88	36.51	8.77	0.41
— P5	N.S.	<0.001	N.S.	<0.001
— P3	N.S.	<0.001	N.S.	<0.001
— P6	N.S.	<0.001	N.S.	<0.001

P1 Group (I) Versus Control Group.
P2 Group (II) Versus Control Group
P3 Group (III) Versus Control Group
P4 Group (I) Versus Group (II)
P5 Group (I) Versus Group (III)
P6 Group (II) Versus Group (III)

Table (2) : Correlation between Systolic, Diastolic and Mean Blood Pressure with Plasma TXB2 and 6.K.PGF1 α Levels in Patients.

Group (I)	Plasma TXB2 Level		Plasma 6.K.PGF1 αLevel	
	r	P	r	P
Systolic blood pressure	0.68	< 0.001	0.68	< 0.001
Diastolic blood pressure	0.72	< 0.001	0.70	< 0.001
Mean blood pressure	0.76	< 0.001	0.74	< 0.001
Group (II)	**Plasma TXB2 Level**		**Plasma 6.K.PGF1 αLevel**	
	r	P	r	P
Systolic blood pressure	0.92	< 0.001	0.82	< 0.001
Diastolic blood pressure	0.92	< 0.001	0.80	< 0.001
Mean blood pressure	0.94	< 0.001	0.83	< 0.001
Group (III)	**Plasma TXB2 Level**		**Plasma 6.K.PGF1 αLevel**	
	r	P	r	P
Systolic blood pressure	0.86	< 0.001	0.69	< 0.001
Diastolic blood pressure	0.86	< 0.001	0.69	< 0.001
Mean blood pressure	0.88	< 0.001	0.71	< 0.001

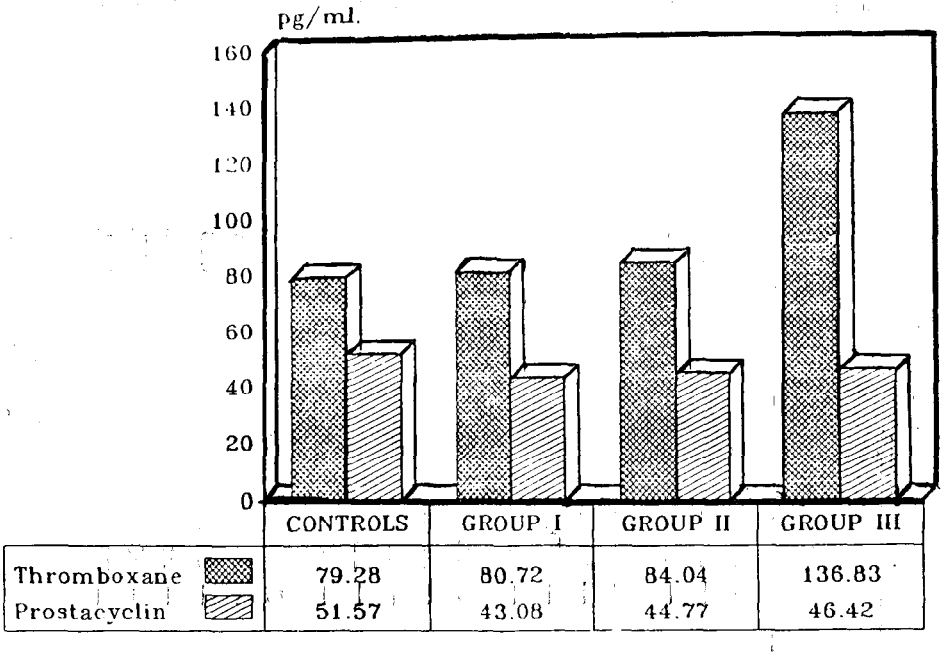

Fig. 1. Plasma thromboxane and prostacyclin in normals & hypertensives.

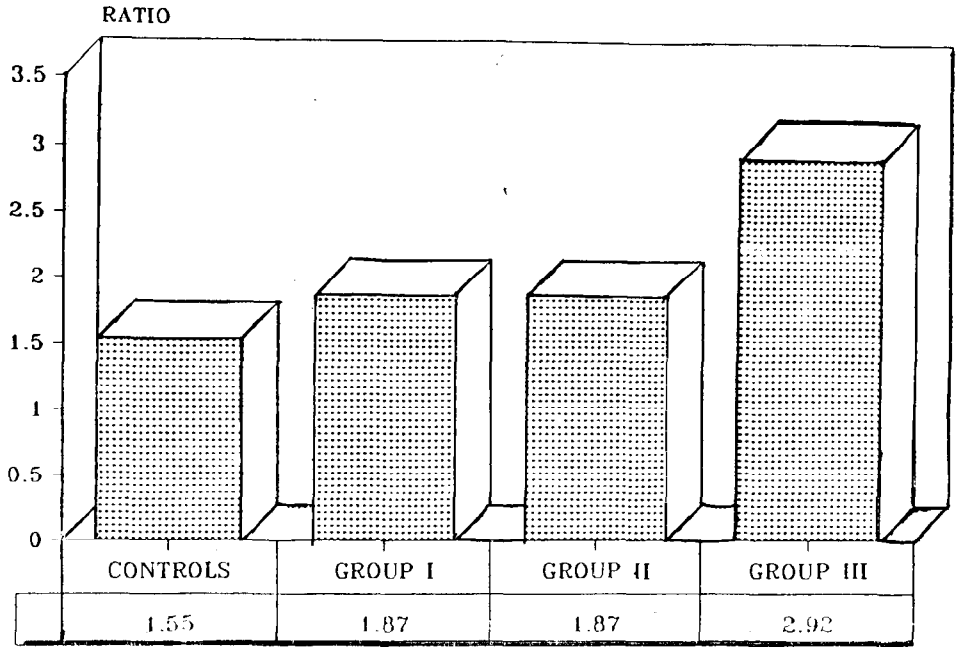

Fig. 2. Ratio of thromboxane to prostacyclin in normals & Hypertensives.

Discussion

Hypertensive vascular disease is probably the most important puplic health problem in developed countries. It is common, asymptomatic, and unless treated it often leads to lethal complications. It is characterized by increased peripheral resistance and an increased incidence of arterial occlusive disease. The pathophysiology of these processes is incompletely understood but abnormal prostaglandin systhesis has been implicated[**6**].

McGiff and Vane[**7**], suggested that prostaglandins participate in the regulation of blood pressure by exerting local actions within the kidney and within the arterial walls, and suggested that disordered prostacyclin synthesis could therefore contribute to the pathophysiology of hypertension. These ideas gained support from observations that cycloxygenase inhibitors increase blood pressure in hypertensive patients especially those receiving antihypertensive treatment[**8,9**]. Conversely, dietary supplementation with polyunsaturated fatty acids that may augment vasodilator prostaglandin synthesis have been reported to lower blood pressure[**10,11**].

The discovery and biological properties of thromboxane A2 (TXA2) and prostacyclin (PGI2) raised the possibility that increased TXA2 synthesis or reduced PGI2 synthesis could contribute to the pathophysiology of essential hypertension[**6**].

Thromboxane A2 (TXA2) and prostacyclin (PGI2) have opposing effects on

platelets and vascular smooth muscles. While TXA2 causes vasoconstriction and platelet aggregation, PGI2 is a vasodilator, a natriuretic, and a potent inhibitor of platelet aggregation. Thus, an imbalance in their biosynthesis could influence both vascular tone and predisposition to thrombosis[2].

In our study, patients with uncomplicated hypertension (group I), showed no significant difference in the mean plasma TXB2 level in hypertensive patients as compared to control group. On the other hand, the mean plasma 6-Keto-PGF1 α level was significantly lower ($P < 0.05$). Also the mean value of the ratio TXB2/6.K.PGF1 α was significantly higher ($P < 0.001$) in uncomplicated hypertensive patients (1.87 ± 0.11) as compared to controls (1.55 ± 0.07), (Table 1).

Hornych et al.[12] observed increased TXB2 level in patients with mild essential hypertension. However, our results are in agreement with the findings reported by Campbell et al.[13]; Minuz et al.[2] and Somova & Mufunda[14]. Low 6.K PCF1 α level in our hypertensive patients is in agreement with Minuz et al.[2]; Somova & Mufunda[14] and Lemne et al.[15] but differs from data obtained by Knapp & Fitzgerald[10] who observed no consistent difference in normotensives and hypertensives.

Fitzgerald et al[16]; Lotfy[17] and Hawkins et al[18] concluded that decreased PGI2 formation might play a part in pregnancy - induced hypertension. The present study provides evidence that this may also be true for essential hypertension.

Several vasoconstrictor hormones, including angiotensin II, vasopression and epinephrine, stimulate PGI2 synthesis by cultured vascular cells and by intact vascular tissue in vitro[19]. Those least able to increase PGI2 synthesis adequately in response to pressor stimuli would be expected to manifest high blood pressures[20 & 21].

The relative deficiency of PGI2 compared to TXA2 noted in the present study, could influence not only vascular resistance, but also platelet aggregation and hence the predisposition to arterial thrombosis in patients with essential hypertension. Similar conclusion was reported by Somova & Mufunda[14]; Lemne et al[15] and Uehara et al[22].

In hypertensive patients complicated by ischemic heart disease (group II), our results showed no significant difference in the mean plasma TXB2 level and both control group and group I patients. There was also no significant difference in mean plasma 6-K-PGF1 α level between group II patients and both control group and group I patients. Unexpectedly, the mean value of the ratio TXB2/6-K-PGF1 α was significantly higher ($P < 0.001$) in group II patients (1.87 ± 0.16) as compared to control group (1.55 ± 0.07) and was insignificantly altered from that of group I patients (1.87 ± 0.11).

Several studies have been performed to evaluate the role of TXA2 and/or PGI2 in coronary artery disease, however they were concerned with acute coronary syndromes. Fitzgerald et al[23] observed elevated urinary levels of TXA2 derived

products in patients with unstable angina or acute myocardial infaraction. Similar findings were reported later[**24,25,26**].

The fact that none of the patients included in our study had an acute event at the time of the study can explain the non significant difference observed.

Yet in group II the ratio TXB2/6.K.PGF1 α was significantly higher than control whether this is merely due to the associated hypertension or it represents marker for cardiovascular risk this needs further assessment. According to Akimova, [**27**], the increased ratio of TXB2/6.K.PGF1 α in normotensive children and adolescents represents a high risk of developing ischemic heart disease.

In hypertensive patients complicated by cerebral infarction (group III), our results showed that the mean plasma TXB2 level was significantly higher in group III patients when compared to either control group, group I patients, or group II patients, ($P < 0.001$). There was no significant difference observed in the mean plasma 6,K.PGF1 α level between group III patients and either control group, group I, or group II patients. However, the mean value of the ratio TXB2/6.K.PGF1 was significantly higher in group III patients (2.92 ± 0.41) as compared to either control group (1.55 ± 0.07), group I patients (1.87 ± 0.11), or group II patients (1.87 ± 0.16) ($P < 0.001$). TXA2 as a potent platelet aggregator and vasoconstrictor agent can reduce cerebral blood flow with the subsequent conversion of transient ischemic attack into a completed stoke[**28**]. The use of Prophylactic aspirin, is strongly supported by the results of multiple clinical studies[**28,29**].

The significantly higher level of plasma TXB2 in hypertensive patients with acute cerebral infarction is in agreement with results reported by Patrono et al[**29**]; Koudstaal et al[**28**] and Fisher[**30**].

Our patients presented with acute cerebral infarction which can explain why plasma TXB2 level was significantly high in these patients while it was not significantly high in hypertensive patients presenting with chronic coronary artery disease. This can also illuminate the role of TXA2 as a potent platelet aggregator and vasoconstrictor agent. In group III patients we suggest that the absence of rise in the plasma 6.K.PGF1 α level denotes an inadequate compensatory mechanism to guard against the raised TXB2 level.

The significantly higher TXB2/6.K.PGF1 α ratio in group III confirms the importance of this ratio as a marker of increased vascular tone and predisposition or even development of arterial thrombosis. It is explained by very high plasma TXB2 level found in group III patients and can illuminate the role of the imbalance in biosynthesis of TXA2 and PGI2 in the culmination of acute thrombotic episodes. Green and Vesterquist[**31**] considered the ratio TXB2/6.K.PGF1 α as a very good marker indicating a risk for subsequent acute thrombotic episodes.

In our study, the arterial blood pressure (systolic, or diastolic or mean) was positively correlated with both plasma TXB2 and 6.K.PGF1 α levels in the three

tested groups. Also, the mean plasma TXB2 was positively correlated with the plasma 6.K.PGF1 α in the three tested groups as well as the control group. These findings support the theory suggesting that prostacyclin has a compansatory role counteracting increased thromboxane A2 biosynthesis.

In the present study there was no significant difference observed in the mean plasma renin activity among the investigated groups.

So we can conclude that several pressor stimuli tend to elevate the blood pressure. The vascular tissue responds to these stimuli by increasing the biosynthesis of vasodilator prostacyclin. Those defective PGI2 synthesis would be expected to have high blood pressure (group I). Hypertensive patients having chronic complications (group II - stable coronaty artery disease) remain stable so long that there is no enhanced TXA2 biosynthesis. During states of enhanced TXA2 biosynthesis, a relative deficiency of PGI2 compared to increased TXA2, could enhance both vasospasm and platelet aggregation and hence the predisposition to arterial thrombosis (group III - acute cerebral infarction).

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